Kidney International, Vol. 40 (1991), pp. 1098–1102

CLINICAL INVESTIGATION

Pregnancy in IgA nephropathy

SHINICHI ABE

Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan

Pregnancy in IgA nephropathy. The impacts of IgA nephropathy and pregnancy on each other were evaluated in 118 women who conceived 168 times between 1970 and 1988. Rates of spontaneous abortion, normal delivery, live birth and perinatal death were 9, 66, 87 and 4%, respectively. Infants born to women with glomerular filtration rates (GFR) lower than 70 ml/min prior to conception had a higher perinatal mortality rate (14% vs. 3%, $P < 0.001$). This was also true if pre-pregnancy blood pressures were consistently higher than 140/90 mm Hg (33% vs. 1%, $P < 0.001$). These were the figures for the whole 18 year period, but stratification of the data revealed that most adverse results occurred in the 1970's, during which the perinatal death rate was 9%, while it was 0% in the 1980's. Eighty-five women were followed for three years or more. At final follow-up, the rates of decrease in GFR, and increases in blood pressure and proteinuria were 19, 11 and 7%, respectively. In most patients the natural history of IgA nephropathy was similar to that of women who had not experienced pregnancy, but there were five instances where gestation seemed to accelerate functional loss, with rapid development of end-stage or near end-stage renal failure. Most women with IgA nephropathy should anticipate few problems with pregnancy, if they are normotensive and their preconception GFR exceeds 70 ml/min. The gestation in such instances should have little influence on the natural history of their nephropathy.

IgA nephropathy is one of the most common chronic glomerulonephritic syndromes and frequently affects women at the peak of their childbearing years. In this latter respect, the nephrologist is often consulted concerning the advisability of conceiving or to assist in the management of pregnancies already in progress in women who have IgA nephropathy. The specific questions are: 1) whether the pre-existing IgA nephropathy adversely influences the course of pregnancy including fetal outcome, and 2) whether pregnancy has a negative effect on the natural course of IgA nephropathy including long-term prognosis.

The answers to these questions have been a source of controversy among nephrologists for some time [1–12], but investigators have recently been moving toward a consensus. Divergent opinions might be due to the number of patients studied being too small, inclusion of women with decreased renal function and/or hypertension, and the decade in which the investigation was performed. Differences in obstetrical and renal care at various localities, disparate ways of collecting and presenting the data, and differences in the natural history of the disease among ethnic populations could also account for the variances. In the current study, the reciprocal influences of pregnancy and IgA nephropathy were studied by reviewing a large number of patient records. To minimize the effects of the aforementioned variables, the data were collected from several university hospitals throughout Japan.

Received for publication February 28, 1991
and in revised form July 11, 1991
Accepted for publication July 11, 1991

Methods

Patients

The clinical data for this study were collected from nine university hospitals and their affiliates in Japan. A large part of the data were also provided by Dr. S. Tojo, Director of the Special Research Group for "progressive renal impairment" sponsored by the Japanese Ministry of Health and Welfare.

The clinical course of 118 women who underwent 168 pregnancies from 1970 through 1988, whose underlying renal disease had been diagnosed as IgA nephropathy according to WHO criteria [13], were analyzed. In 110 women (93%), renal biopsy had been performed prior to pregnancy. The other 8 (7%) were biopsied after delivery or abortion, because of either a previous history of chronic glomerulonephritis or urinary abnormalities observed during gestation which persisted after delivery or termination of pregnancy. Women who underwent elective abortions were excluded from this survey, as the definitive reason for the termination was not clear in retrospect.

After delivery or termination of pregnancy, 85 patients who remained in follow-up for at least three years were assessed in terms of the effects of pregnancy on the underlying IgA nephropathy. To discern whether observed declines in GFR reflected the natural course of the underlying nephropathy or were an adverse effect of pregnancy, the course of renal function in pregnant ($N = 32$) and nonpregnant women ($N = 30$), whose age and renal function at the time of biopsy were in the same range, were compared.

Clinical data such as GFR and blood pressure obtained at the time of biopsy were correlated with obstetrical and long-term renal outcomes. In the women who conceived more than six months after biopsy, clinical parameters obtained no longer than six months before conception were used.

Prematurity was defined as a gestation of less than 37 weeks, low birth weight as less than 2,500 g, and perinatal death rate as the sum of stillbirths and deaths within one week of birth [14].

GFR was measured by 24-hour endogenous creatinine clearance and the obtained values were corrected for preconception body weight and a surface area of 1.73 m^2. A woman whose blood pressure was consistently higher than 140/90 mm Hg was

Table 1. Results of pregnancies with IgA nephropathy

	No. of pregnant women	No. of pregnancies	Deliveries %			Perinatal deaths		Spontaneous abortions
			Normal	Abnormal	Live infants	%		
1970–1980	63	79	53 (67%)	13 (16%)	66 (84%)	7 (9%)	b	6 (8%)
1981–1988	69	89	58 (65%)	22 (25%)	80 (90%)	0 (0%)	b	9 (10%)
Total	118[a]	168	111 (66%)	35 (21%)	146 (87%)	7 (4%)		15 (9%)

Perinatal death rate for the whole Japanese population (per 1,000 live births) as reported by the Japanese Ministry of Health and Welfare

1975	1980	1985
16.0 (1.6%)	11.7 (1.2%)	8.0 (0.8%)

[a] Fourteen women conceived in both the 1970's and 1980's
[b] $P < 0.01$

defined as hypertensive. Those whose pressures were controlled with medication were also considered to be hypertensive. When compared with prepregnancy levels, decreased renal function was defined as a 50% or greater increase in serum creatinine level and/or a 20 ml/min or more decrease in GFR, increased blood pressure as an elevation of at least 30/20 mm Hg and increased proteinuria as a doubling of protein excretion based on 24-hour urine collection.

For statistical analysis, the χ^2-test and t-test were used. $P < 0.05$ was considered significant. The values in tables are expressed as the mean ± 1 SD.

Results

The outcomes of all 168 pregnancies in 118 women with IgA nephropathy are depicted in Table 1. A total of 146 (87%) of these pregnancies resulted in the birth of a live infant. Complications, which affected 35 (21%) of these deliveries, included low-birth weight ($N = 20$), often in the setting of prematurity ($N = 3$), polyhydramnios ($N = 1$), premature placental abruption ($N = 1$), severe post-partum hemorrhage ($N = 1$) and preeclampsia ($N = 10$).

In comparing the rates of perinatal death and live births between the 1970's and 1980's, the drop in the former from 9% to 0% is clearly significant ($P < 0.01$). Abnormal deliveries increased from 16% to 25%, producing an increase in total live births (from 84% to 90%), but neither value was statistically significant.

The perinatal death rates are compared with the overall perinatal death rates, reported by the Japanese Ministry of Health and Welfare for the same time periods, that is, 1975 and 1985 (Table 1) [14]. The 1970 to 1980 perinatal death rate in this series is significantly higher than that of the general population (9% vs. 1.6%), in contrast to the 1981 to 1988 rate which was 0%.

Table 2 shows the relationships between the clinical parameters of blood pressure, both systolic and diastolic, and GFR before conception and obstetrical outcome. The group which experienced complications and/or perinatal losses had significantly higher preconception blood pressures than the normal delivery group.

In terms of blood pressure, 90% of pregnancies in normotensive women were successful. However, hypertensive women had a perinatal death rate of 33% ($P < 0.001$). There were also significantly fewer normal deliveries and a lower live birth rate in the latter group than in the normotensive women (Fig. 1).

Table 2. Relationship between clinical parameters at time of biopsy and obstetrical outcome

	Normal deliveries	Abnormal deliveries	Perinatal deaths	Spontaneous abortions
Blood pressure				
Systolic *mm Hg*	117 ± 11	125 ± 17 [b]	133 ± 29 [b]	118 ± 9
Diastolic *mm Hg*	71 ± 9	77 ± 13 [a]	82 ± 18 [b]	70 ± 6
GFR *ml/min*	90 ± 16	93 ± 20	94 ± 17	97 ± 18

[a] $P < 0.05$
[b] $P < 0.01$

The degree of renal functional impairment also influenced obstetrical outcome. All women had a GFR >60 ml/min. When GFR was greater than 70 ml/min before conception the perinatal death rate was 3%, while if GFR was less than 70 ml/min, the rate increased to 14% ($P < 0.001$; Fig. 1).

The long-term effect of pregnancy on the underlying IgA nephropathy is summarized in Table 3 and Figure 2, which illustrate the status at final follow-up of 85 gravidas monitored for at least three years after pregnancy. The rates of decrease in GFR and increase in blood pressure and proteinuria were 19%, 11% and 7%, respectively. These rates did not differ significantly between pregnancies which occurred in the 1970's versus the 1980's (Table 3). However, as shown in Figure 2, in patients who were hypertensive or whose GFR was lower than 70 ml/min before conception, these rates were obviously higher. For example, among those who had low GFR before conception, one half (5 out of 10) experienced a further significant decline. For two women this deterioration necessitated regular hemodialysis. As to the effect on blood pressure, a significant increase was found at follow-up in 30% (3 out of 10). The same

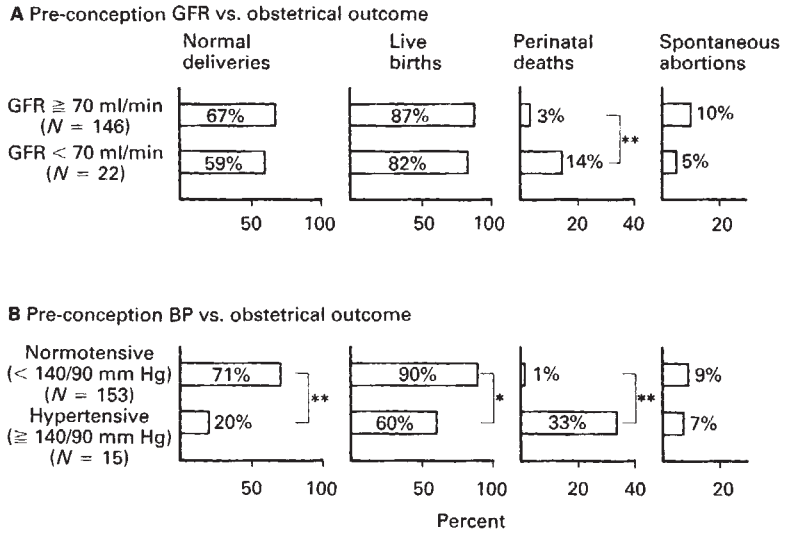

Fig. 1. *Relationships between preconception GFR, blood pressure and obstetrical outcome.* $*P < 0.01$; $**P < 0.001$.

Table 3. Long-term effect of pregnancy on underlying IgA nephropathy

Final conception	No. of pregnant women	Decrease in GFR	Increase in BP	Increase in proteinuria
		%		
1970–1980	36	7 (19%)	5 (14%)	3 (8%)
1981–1985	49	9 (18%)	4 (8%)	3 (6%)
Total	85	16 (19%)	9 (11%)	6 (7%)

was true for those patients whose blood pressure was consistently higher than 140/90 mm Hg before conception.

Table 4 compares the course of renal function in pregnant and non-pregnant women with IgA nephropathy. From this table it is clear that the renal outcome for the majority of women who underwent pregnancy was very similar to that of controls. At the end of follow-up there was no difference in GFR between the pregnant and non-pregnant groups. However, five of the women who experienced pregnancy progressed to end stage or near end-stage renal failure, three requiring regular hemodialysis between 1.5 and 3 years after delivery. Two of the controls ultimately required hemodialysis, but not until five years after the initial determination of renal function. The clinical data of these five patients are shown in Table 5.

Although all of these women were initially normotensive and had GFR above 70 ml/min, those experiencing significant deterioration could be distinguished from the rest of the patient population on the basis of their pre-conception biopsy results. All five had been histologically diagnosed as having moderate or advanced diffuse proliferative glomerulonephritis with widespread tubulointerstitial lesions such as tubular atrophy, interstitial cell infiltration and fibrosis along with arteriolosclerosis. In contrast, neither widespread tubulointerstitial lesions nor significant arteriolosclerosis had been observed in women who had good obstetrical results, even though about 30% had been diagnosed as having moderate diffuse proliferative glomerulonephritis.

Discussion

Managing pregnancy in patients with underlying glomerulonephritis is becoming more important for clinicians, as nowadays many patients are willing to take on the challenge of pregnancy. Up-to-date information concerning the effects of gestation on long-term outcome is necessary. Several studies on this topic have been published [1–12] but, as Packham et al [9] have stressed, only a few have dealt with large series of patients, with but a single, histologically confirmed, glomerular disorder. IgA nephropathy is one of the most common forms of glomerulonephritis affecting women of child-bearing age. Access to large numbers of women with this disease, who have conceived, will provide valuable information which should help nephrologists counsel women with IgA nephropathy who are considering pregnancy, or who are already pregnant.

In most recent studies the perinatal death rates have been between 4% and 10% [6–8, 10], with the exception of the 23% rate calculated from the data of Packham et al [9]. Elective abortions were not included in these figures. Packham et al's high rate may be due to differences in patient population as well as the degree of renal dysfunction. In this study all patients had GFR greater than 60 ml/min at initial check-up, that is, women with moderately or severely decreased renal function were not included. The previously reported rate of 10% [6], based on data from 30 of the patients included in the present study, has been reduced to 4%. Still the rate of 4% is excessive, especially when compared with that of the Japanese population as a whole [14]. However, as mentioned previously, even the rate of 4% is exaggerated, for in the past decade the rate has decreased to zero. This probably reflects advances in prenatal care by the obstetrician-nephrologist team, as well as in neonatal care nurseries.

As illustrated in Figure 1, women with normal or slightly impaired renal function generally experienced a favorable outcome. In addition, most normotensive women had good results. However, as has been pointed out by several investigators in

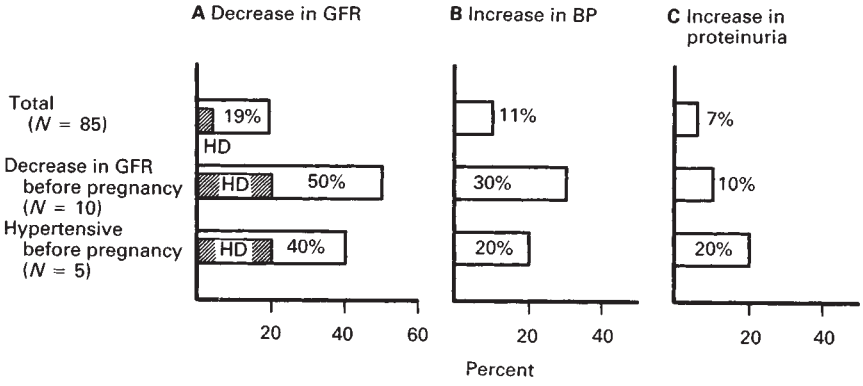

Fig. 2. *Long-term effect of pregnancy on underlying IgA nephropathy: status at final follow-up.* Abbreviation HD is receiving regular hemodialysis.

Table 4. Course of GFR in pregnant and non-pregnant women with IgA nephropathy

	At biopsy	1	2	3	4	5
		years				
Pregnant *ml/min* ($N = 32$)	81 ± 13	91 ± 19	85 ± 17	81 ± 16	73 ± 22	69 ± 26
Non-pregnant *ml/min* ($N = 30$)	88 ± 16	86 ± 19	80 ± 15	78 ± 18	72 ± 21	69 ± 26

In the above data, all pregnancies occurred within 2 years of the renal check-up with biopsy. Part of the data for non-pregnant women provided by Kobayashi Y and Moriya R.

Table 5. Clinical parameters of patients whose renal functional loss progressed after delivery

Age at biopsy *years*	GFR before pregnancy *ml/min*	GFR at final follow-up *ml/min*	BP before pregnancy *mm Hg*	Proteinuria before pregnancy *g/day*	Biopsy findings: Degree of glomerular proliferation	Biopsy findings: Tubulo-interstitial lesions	Biopsy findings: Arteriolo-sclerosis
25	85	22	124/88	1.5	moderate	(++)	(−)
24	100	36	118/70	0.5	moderate	(+)	(−)
26	70	HD	140/90	0.9	moderate	(+)	(+)
25	70	HD	122/80	1.0	advanced	(++)	(+)
23	78	HD	130/86	1.2	advanced	(++)	(+)
(Average preconception parameters; 32 patients)							
25 ± 3	81 ± 13	69 ± 26	119 ± 10/74 + 9	0.6 ± 0.4			

Abbreviation HD is receiving regular hemodialysis.
Degree of glomerular proliferation: minor, mild, moderate, advanced.
Degree of tubulointerstitial lesions: −, +, ++.
Degree of arteriolosclerosis: −, +, ++.

this field, women with decreased renal function and/or hypertension tend to have more obstetrical complications [1, 2, 6–8, 12]. Thus, it is advisable for patients planning to attempt pregnancy to have normal blood pressure and a GFR greater than 70 ml/min before conception, and if in such women the disease appears stable, they can be advised that with meticulous prenatal care the chance of delivering a healthy infant is excellent.

Regarding the effect of pregnancy on the underlying IgA nephropathy, the overall rates of decrease in GFR, and increases in blood pressure and proteinuria at final follow-up were not significantly higher than those of IgA nephropathy patients who had never undergone pregnancy. However, in patients who were hypertensive or who had GFRs below 70 ml/min before conception, the long-term prognosis was less optimistic.

In order to evaluate whether the small decrements in GFR observed at follow-up reflected the natural course of the renal disease or represented an adverse effect of pregnancy, the course of renal function in a group of patients was compared with that of women with IgA nephropathy who had never been pregnant. These groups were matched for age and GFR at the start of analysis and their renal function was monitored over the next five years. As shown in Table 4, there were no significant differences between the two groups. These results agree with those of Jungers et al [12] who concluded that pregnancy had no general influence on the course of IgA nephropathy.

A minority of patients ($N = 5$) progressed to end stage or near end-stage renal failure. It was of interest that these women could be distinguished from the rest of the patient population on the basis of their pre-conception biopsy results [6]. Although their GFR were equal to or higher than 70 ml/min at the initial check-up, they had severe histological impairment not only in the glomeruli but also in arterioles, tubules and the interstitium. Packham et al [15] reported a very high rate of IgA nephropathy

with superimposed focal and segmental proliferative lesions in their patients who eventually experienced significant deterioration in renal function. In addition, obstetrical complication and fetal loss rates were very high among these women. In the majority of patients, however, pregnancy does not appear to worsen underlying IgA nephropathy.

In conclusion, patients with IgA nephropathy will probably tolerate pregnancy well and it will most likely not have an adverse effect on the course of their underlying disease, if blood pressure is normal and GFR more than 70 ml/min before conception. In cases with hypertension, however, the rate of live birth is extremely low if hypertension exists before pregnancy and/or is not controlled during gestation.

Acknowledgments

The author is very grateful to Dr. Marshall D. Lindheimer and Dr. John M. Davison for reviewing the manuscript. The following doctors generously provided data used in this study: Dr. S. Tojo (The Director of the Special Research Group for "Progressive Renal Impairment" sponsored by the Japanese Ministry of Health and Welfare, Tsukuba Gakuen Hospital); Drs. O. Sakai and T. Kitajima (Jikei University); Drs. M. Narita and T. Koyama (The University of Tsukuba); Drs. T. Takuma and N. Nakanishi (Tokyo Women's Medical College); Dr. T. Ideura (Showa University Fujigaoka Hospital); Drs. Y. Kobayashi and R. Moriya (Kitasato University); Dr. Y. Nagai (Toho University); Dr. Y. Amagasaki (Yokohama City Nanbu Hospital); Dr. S. Iyori (Hiratsuka City Hospital).

Reprint requests to Shinichi Abe, M.D., Department of Internal Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo, 160, Japan.

References

1. KATZ AI, DAVISON JM, HAYSLETT JP, SINGSON E, LINDHEIMER MD: Pregnancy in women with kidney disease. *Kidney Int* 18:192–206, 1980
2. DAVISON JM, KATZ AI, LINDHEIMER MD: Kidney disease and pregnancy: Obstetric outcome and long-term renal prognosis. *Clin Perinatol* 12:497–519, 1985
3. KATZ AI, LINDHEIMER MD: Does pregnancy aggravate primary glomerular disease? *Am J Kidney Dis* 6:261–265, 1985
4. BECKER GJ, FAIRLEY KF, WHITWORTH JA: Pregnancy exacerbates glomerular disease. *Am J Kidney Dis* 6:266–272, 1985
5. HAYSLETT JP: Pregnancy does not exacerbate primary glomerular disease. *Am J Kidney Dis* 6:273–277, 1985
6. ABE S, AMAGASAKI Y, KONISHI K, KATO E, SAKAGUCHI H, IYORI S: The influence of antecedent renal disease on pregnancy. *Am J Obstet Gynec* 153:508–514, 1985
7. JUNGERS P, FORGET D, HENRY-AMAR M, ALBOUZE G, FOURNIER P, VISCHER U, DROZ D, NOEL L, GRUNFELD J: Chronic kidney disease and pregnancy. *Adv Nephrol* 15:103–141, 1986
8. SURIAN M, IMBASCIATI E, COSCI P, BANFI G, BARBIANO DI BELGIOJOSO G, BRANCACCIO D, MINETTI L, PONTICELLI C: Glomerular disease and pregnancy. *Nephron* 36:101–105, 1984
9. PACKHAM DK, NORTH RA, FAIRLEY KF, WHITWORTH JA, KINCAID-SMITH P: IgA glomerulonephritis and pregnancy. *Clin Nephrol* 30:15–21, 1988
10. BARCELÓ P, LÓPEZ-LILLO J, CABERO L, DEL RIO G: Successful pregnancy in primary glomerular disease. *Kidney Int* 30:914–919, 1986
11. KINCAID-SMITH P, FAIRLEY KF: Renal disease in pregnancy. Three controversial areas: Mesangial IgA nephropathy, focal glomerular sclerosis (focal and segmental hyalinosis and sclerosis), and reflux nephropathy. *Am J Kidney Dis* 9:328–333, 1987
12. JUNGERS P, FORGET D, HOUILLIER P, HENRY-AMAR M, GRUNFELD JP: Pregnancy in IgA nephropathy, reflux nephropathy, and focal glomerular sclerosis. *Am J Kidney Dis* 9:334–338, 1987
13. CHURG J, SOBIN LH: *Renal disease. Classification and Atlas of Glomerular Diseases*. Igaku-shoin, Tokyo, 1982
14. NATIONAL HYGIENIC STATISTICS ISSUED BY THE JAPANESE MINISTRY OF HEALTH AND WELFARE "*Kosei no Shihyo*" (in Japanese). 36 Suppl: 71–75, 1989
15. PACKHAM D, WHITWORTH JA, FAIRLEY KF, KINCAID-SMITH P: Histological features of IgA glomerulonephritis as predictors of pregnancy outcome. *Clin Nephrol* 30:22–26, 1988